

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for oral delivery of a physiologically active peptide agent comprising a therapeutically effective amount of said active peptide, wherein said active peptide is amidated at a location that  
5 is not naturally amidated.

2. The pharmaceutical composition of claim 1 further comprising at least one pharmaceutically acceptable pH-lowering agent and/or protease inhibitor.

3. The pharmaceutical composition of claim 2 further comprising an acid resistant protective vehicle effective to transport said pharmaceutical composition through the stomach of a patient while preventing contact between said  
5 active peptide agent and stomach proteases.

4. The pharmaceutical composition of claim 1, wherein said active peptide agent is amidated at the C-terminal end.

5. The pharmaceutical composition of claim 4, wherein said peptide is prepared as glycine-extended precursor and subsequently converted to a C-terminal amide group.

6. The pharmaceutical composition of claim 1, wherein said active peptide comprises an amino acid that contains an amidated side chain.

7. The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5.

8. The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 3.5.

9. The pharmaceutical composition of claim 2, wherein said protease inhibitor is a stomach and/or intestine protease inhibitor.

10. The pharmaceutical composition of claim 2, wherein said protease inhibitor inhibits an enzyme selected from the group consisting of pepsin, trypsin, chymotrypsin, elastase, kallikrein and carboxypeptidase.

11. The pharmaceutical composition of claim 1, wherein said active peptide agent is linked to a membrane translocator which is capable of being at least partially cleaved in vivo by an enzyme.

12. The pharmaceutical composition of claim 3, wherein

said protective vehicle is present at a weight which is no more than 30% of the weight of the remainder of said pharmaceutical composition.

13. The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is no more than 20% of the weight of the remainder of said pharmaceutical composition.

14. The pharmaceutical composition of claim 3, wherein said protective vehicle is present at a weight which is between 10% and 20% of the weight of the remainder of said pharmaceutical composition.

15. The pharmaceutical composition of claim 3, wherein said protective vehicle is sufficient to prevent breakdown of said pharmaceutical composition in 0.1N HCl for at least two hours, yet permits complete release of all contents of  
5 said pharmaceutical composition within 45 minutes after pH is increased to 6.3 in a dissolution bath in which said composition is rotating at 100 revolutions per minute.

16. The pharmaceutical composition of claim 3 further containing at least one absorption enhancer effective to promote bioavailability of said active agent.

17. The pharmaceutical composition of claim 16, wherein said absorption enhancer is a surface active agent.

18. The pharmaceutical composition of claim 17, wherein said surface active agent is absorbable or biodegradable.

19. The pharmaceutical composition of claim 17, wherein said surface active agent is selected from the group consisting of acylcarnitines, phospholipids and bile acids.

20. The pharmaceutical composition of claim 19, wherein said enhancer is an acyl carnitine.

21. The pharmaceutical composition of claim 20; further including a sucrose ester.

22. The pharmaceutical composition of claim 16, wherein said absorption enhancer is a surface active agent selected from the group consisting of (i) an anionic agent that is a cholesterol derivative, (ii) a mixture of a  
5 negative charge neutralizer and an anionic surface active agent, (iii) non-ionic surface active agents, and (iv) cationic surface active agents.

23. The pharmaceutical composition of claim 16, wherein said absorption enhancer is selected from the group consisting of a cationic surfactant and an anionic surfactant that is a cholesterol derivative.

24. The pharmaceutical composition of claim 16,

wherein said pharmaceutical composition includes at least two absorption enhancers, one of which is a cationic surface active agent, and another of which is an anionic surface  
5 active agent that is a cholesterol derivative.

25. The pharmaceutical composition of claim 24, wherein said anionic surface active agent is an acid-soluble bile acid.

26. The pharmaceutical composition of claim 1, further comprising an amount of a second peptide that is not a physiologically active peptide effective to enhance bioavailability of said peptide active agent.

27. The pharmaceutical composition of claim 3, further comprising a water soluble barrier that separates said pH-lowering agent from said protective vehicle.

28. The pharmaceutical composition of claim 2, wherein said composition includes at least one pH-lowering agent that has a pKa no higher than 4.2.

29. The pharmaceutical composition of claim 2, wherein at least one pH-lowering agent has a solubility in water of at least 30 grams per 100 milliliters of water at room temperature.

30. The pharmaceutical composition of claim 3, wherein

all ingredients other than said protective vehicle are uniformly dispersed.

31. The pharmaceutical composition of claim 30, wherein said pharmaceutical composition comprises granules containing a pharmaceutical binder and, uniformly dispersed in said binder, said pH-lowering agent, said absorption enhancer and said peptide active agent.

32. The pharmaceutical composition of claim 16, wherein said composition is a solid dosage form wherein a weight ratio of said pH-lowering agent to said absorption enhancer is between 3:1 and 20:1.

33. The pharmaceutical composition of claim 16, wherein said composition is a solid dosage form wherein the weight ratio of said pH-lowering agent to said absorption enhancer is between 5:1 and 10:1.

34. The pharmaceutical composition of claim 2, wherein said pH-lowering agent is selected from the group consisting of citric acid, tartaric acid and an acid salt of an amino acid.

35. The pharmaceutical composition of claim 2, wherein said pH-lowering agent is present in an amount not less than 300 milligrams.

36. The pharmaceutical composition of claim 35, wherein said pH-lowering agent is present in an amount which is not less than 400 milligrams.

37. The pharmaceutical composition of claim 1, wherein said peptide agent is human glucagon-like peptide 1, human glucagon-like peptide 2 or analog thereof.

38. The pharmaceutical composition of claim 1, wherein said peptide agent is salmon calcitonin.

39. The pharmaceutical composition of claim 1, wherein said peptide agent is insulin.

40. The pharmaceutical composition of claim 1, wherein said peptide agent is human parathyroid hormone or analog thereof.

41. The pharmaceutical composition of claim 1, wherein said peptide agent is human parathyroid hormone analog PTH 1-31NH<sub>2</sub>.

42. The pharmaceutical composition of claim 1, wherein said peptide agent is human parathyroid hormone analog PTH 1-34NH<sub>2</sub>.

43. The pharmaceutical composition of claim 3, wherein said protective vehicle is a viscous protective syrup.

44. The pharmaceutical composition of claim 34, wherein a water soluble barrier separates said pH-lowering agent from said protective vehicle.

45. A method for enhancing the bioavailability of an orally delivered physiologically active peptide agent comprising:

- (A) amidating said peptide agent; and
- 5 (B) orally administering said peptide agent.

46. The method of claim 45, wherein said peptide active agent is selectively released together with at least one pH-lowering agent and/or protease inhibitor into a patient's intestine following passage of said peptide active agent, pH-lowering agent and/or protease inhibitor through  
5 said patient's mouth and stomach under protection of an acid resistant protective vehicle which substantially prevents contact between stomach proteases and said peptide agent.

47. The method of claim 45, wherein said active peptide agent has is amidated at the C-terminal end.

48. The method of claim 47, wherein said glycine is prepared as glycine-extended precursor and subsequently converted to a C-terminal amide group.

49. The pharmaceutical composition of claim 45, wherein said active peptide is amidated at an amino acid



side chain.

50. The method of claim 46, wherein said pH-lowering agent is present in said pharmaceutical composition in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5.

51. The method of claim 46, wherein said pH-lowering compound is present in a quantity which, if said composition were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 3.5.

52. The method of claim 46, wherein said protease inhibitor is a stomach and/or intestine protease inhibitor.

53. The method of claim 46, wherein said protease inhibitor inhibits an enzyme selected from the group consisting of pepsin, trypsin, chymotrypsin, elastase, kallikrein and carboxypeptidase.

54. The method of claim 46, wherein the release of said peptide active agent into a patient's intestine is carried out in the presence of at least one absorption enhancer effective to promote bioavailability of said peptide active agent.

55. The method of claim 45, wherein said peptide agent is human glucagon-like peptide 1, human glucagon-like peptide 2, or analog thereof.

56. The method of claim 45, wherein said peptide agent is salmon calcitonin.

57. The method of claim 45, wherein said peptide agent is insulin.

58. The method of claim 45, wherein said peptide agent is human parathyroid hormone or analog thereof.

59. The method of claim 58, wherein said peptide agent is human parathyroid hormone analog PTH 1-31-NH<sub>2</sub>.

60. The method of claim 58, wherein said peptide agent is human parathyroid hormone analog PTH 1-34-NH<sub>2</sub>.

61. The method of claim 45, wherein said peptide agent is luteinizing hormone-releasing hormone.

62. The method of claim 45, wherein said amidation is carried out at a site that is not naturally amidated.

63. The method of claim 45, wherein said enhancement of bioavailability is the result of enhanced intestinal absorption.

64. A pharmaceutical composition for oral delivery of a physiologically active luteinizing hormone-releasing hormone comprising:

(a) a therapeutically effective amount of said  
5 hormone;

(b) at least one pharmaceutically acceptable pH-lowering agent and/or protease inhibitor; and

(c) an acid resistant protective vehicle effective to transport said pharmaceutical composition through the  
10 stomach of a patient while preventing contact between said active peptide agent and stomach proteases.

65. A pharmaceutical composition for oral delivery of human parathyroid hormone analog PTH 1-34-OH comprising:

(a) a therapeutically effective amount of said hormone;

5 (b) at least one pharmaceutically acceptable pH-lowering agent and/or protease inhibitor; and

(c) an acid resistant protective vehicle effective to transport said pharmaceutical composition through the stomach of a patient while preventing contact between said  
10 active peptide agent and stomach proteases.